Reversing Biological Age With Plasma Dilution Transcript

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Introduction to Parabiosis and Longevity

– Welcome to this episode of the reverse inflammaging summit body and mind longevity medicine and I'm your host Dr. Robert Lufkin today. We get to explore the fascinating area of para biosystems transfusions and how these deal with longevity.

And we're fortunate to have a world expert on the area Dr. Irina Conboy high arena. Welcome. – Hello! Hello everybody. – Could you tell us how you came to be so interested in this area and a little bit more about your background?

– So I received my PhD from Stanford where I was in the immunology program. But since my early years my childhood I was interested in aging when I noticed how my grandma looks so different from me and how I am growing and getting taller and at some point will be as old as my grandparents.

So my interest really spend my entire life not just my adult life but my education at Stanford and then Stanford Medical School was focused on understanding immune responses and then understanding what happens to our stem cells as we grow older.

Why is that when we are young we can repair our tissues and organs and when we grow older there's lots of pain. But I hope that answers kind of your introductory question. – Yes. Yes. One thing we ask all our guests on the program is before we, before we get into the details, we always ask what is your overall view of longevity and aging. Why do we age?

What is the overall mechanism there? Do you think? – Well in my opinion and we know what the mechanism is we age because we eat and we breathe. So it is really the oxidative us for election and necessity to make a teepee and then an addition of reactive oxygen species that is inherent in the process that makes us older. So we cannot evolve out of aging in that way. It is really the fundamental processes of our biology that make us old which is called antagonistic method.

Conboyu2019s Background and Aging Theory

– And and well before we get into that so the aging is due to reactive oxygen species that that drive the aging process. Is that what you're saying? – Not just R. O. S. It's just pretty much everything right?

So we have to eat. So you have and you have to breathe and have to make a teepee. And those fundamental processes and ourselves are the ones which then damage they allow us to leave.

But they also damaged us. So which is called antagonistic to Tropea what you need to leave also kills you. So we know that quite well in my opinion. – So an antagonistic pleiotropy, could you explain that again exactly what that is? We haven't heard that before yet in our program.

– So antagonistic pleiotropy means that the same things that are vital for you. For example during embryonic development or simply throughout life or for its production. Exactly the same processes are also deleterious for you. So there is an antagonism and whenever there is antagonistic pleiotropy it's very difficult to impossible to evolve out of that mechanism because it's vital so by the same function.

But the same token it is probably impossible for us to figure out what gene we have to turn off or on to become younger. There will be no such gene, what cells do we have to kill or add to become younger?

What blood factor we can add or remove to become younger because there is no cell or gene or protein that evolved to make us old or sick. They all evolved for good things. And so down the aging they become they become

dis balanced so they are still there but the levels are too high or too low or too noisy.

– So sort of Yeah, that makes sense. So it's sort of if I can recapitulate it sort of that the normal things that are that we've evolved to be value in in youth and help us grow up when we get old, those same mechanisms, those same genes actually causes. – Exactly precipitator is the same process.

The same cells the same mechanisms. But they are just just balanced so it is lack of balance, It is not anything special. It is the overall disarray or dis bounds. – Yeah. And let's let's now turn to parabiosis or you're an expert in that field. Could you tell us a little bit about what it is and some of the initial experiments you did on that.

– I don't think I'm an expert in the field of parabiosis because that procedure was in practice For over almost 200 years or more. Right? But but Dr. Mike convoy and myself applied it to the modern understanding of tissue aging and rejuvenation back in early 2000s.

And so our idea was to test the Beijing a certain stone or is it malleable and plastic? Can we move it backwards and not just allow it to go forward? So when we connected young and organized through the large flaps of their skin, we also connected not just the blood circulation but allowed old animals to benefit from young G. I tract young heart and lungs.

Also old animals now had to exercise because they were running around attached to the young partner. So many events were in place. And the goal of these experiments was not to test if young blood could be a medicine.

There are many manufacturers, but the goal was to see evolved animals with their shortened telomeres and damaged DNA and so forth, could be rapidly and robustly rejuvenated just after a few weeks. And so that's what we found when we looked at muscle liver and in the same studies, we all Also studied the brain.

So back in the early 2000s we found that old animals become functionally and histological e and molecularly younger just after a few weeks of being physically future surgically joined with young animals. And in the same studies, we also discovered that young animals actually become older.

So being connected to an old body for 4-5 weeks is deleterious very, very quickly before there is any accumulation of DNA damage, attrition of telomeres, reactive oxygen species, damage mitochondria and none of that happens.

Parabiosis Experiments and Rejuvenation

So that suggested that aging is plastic and it could go backwards, not just forward and it is a regulated process. So the question was, can we understand the regulation and then adjust the process to our advantage.

– So to to to review that basically the experiment was you took two animals, a young animal and an old animal and you sutured their blood blood streams together essentially. – No, we did not future their bloodstream together. This is not para bio sis okay, What the future is the large blobs of their skin. Okay, So, so then sometimes after the procedure, approximately one week later capillary grows through the skin and the blood becomes shared.

But additional things also become shared. For example, nutrition, normal metabolism of glucose, oxygenation of blood. All of the cells go from young animal to old animal immune cells, right? It exercise and all the animals because they're social, too young have to run around and exercise and they have environmental enrichment.

So their brains might become better. So it is not, it is, you know, not at all, just future. – Okay. Yeah. So the the animals were sutured together, their skin.

Their their tissue sutured together, but not the blood vessels, but eventually the capillaries joined so that they eventually shared blood vessels, but they also shared activity, nutrition. So many other things.

There's so many variables in that. So how did you begin teasing apart? What were the important factors in what were less important? – Yes. So to do that we developed the cleaner experimental system which is the small animal

blood exchange where animals are not sutured together. When we actually perform only blood exchange between young and old miles in about half an hour procedure.

And it is done by the computer operated peristaltic pump. So we can control the percent of exchange the rate of exchange. We know the onset of effects because animals are not connected to each other.

And so it is very similar to the procedure of human blood exchange, but it is miniaturized to mice. So we can test the fact on a brain formation of new neurons, effects on the neuronal plasticity and synapses cognition.

Many, many effects could be interrogated and experimental animals in this way. – So you eliminated the confounding effects of being bound together. So the shared exercise, the shared nutrition and you limit it just just just to the blood.

Just what did you find? – And so what we found is that the results are different from suturing mice together, particularly that all blood dominates over young. So when animals are not sutured and don't run around for four weeks and there is no normalize blood pressure and oxygenation and nutrition.

Then what happens is that young animals become very decrepit and old rapidly after being exchanged with all blood once, one single time. So their exchange without blood ones at 50%.

And obviously there was no time to accumulate aging or damaged or all of these other attributes that people are talking about. This very young mouse but they become much older, particularly in their cognition and neural inflammation and decline in neurogenesis. Much much older very rapidly.

And all the animals do not benefit at all for their brain. After exchange with young blood ones, they benefit somewhat in the muscle and liver, but not in the brain. So that's what we discovered from this well controlled clean experiment that young blood cannot out compete old blood with respect to the brain. And then and then more recently we published work with Judith Campisi lab and her former Postdoc who is now professor in Korea or key Joan Wood, which showed that sin essence can be induced in young animals after one single exchange without blood. So we think about senescent cells as something that happened after many years after accumulation of damage.

But here we started with very young minds that are equivalent to 20 year old people And exchange them to 50% of all blood ones using our approach and then you looked at them at their tissues molecules behavior and they became senescent, they had disobeyed the goalpost of cells in essence was confirmed by many molecular parameters and their kidney and liver and Marcel became older as well as their performance declined. – Well, so many, so many questions. I wonder does that mean we should uh when we give blood transfusions at the hospital, we should note the age of the donor.

So we don't have a mismatch there. – Well, I don't think that for blood transfusion in the hospital, that is the main the main trouble, right? Because because people just get red blood cells or plasma and donors are typically young.

But what we should consider is that many of our concepts and paradigms need restructuring. That aging even in essence is not something that is caused just by damage.

If you buy, you know, if you buy a new pair of shoes and then wear them, it is quite clear that they will linearly get older, right and damaged.

Blood Exchange and Brain Aging

But the thing cannot be said about regenerating systems like mammals like us and mice because we can induce una types of aging and completely young animals.

Before there is any chronological time to accumulate damage. So, these experiments really tell us about the directions of research. If we can identify those factors in cold blood And then diminish them.

Perhaps we can rejuvenate people who are already old. That is the main outcomes of our body work. How can she start with somebody who is old who's 75 years old and then make that person not grow older but start gradually getting younger. That is what can go laboratories pursuing – That's so exciting. It calls into question the whole idea of aging being just a function of wear and tear over time.

So so now we're at the place where you you're transfusing blood, you're no longer suturing the animals together. And that raises as you say, a whole bunch of new questions. So what was the next step you did to to further differentiate or further determine what was it about the the old blood that made the young mice old and and what did you learn from then on?

– So because we have this small animal blood exchange procedure and voice we can ask many, many more questions that could be asked with para bios is for example, we don't have to exchange young or old animal with each other blood.

We can exchange them with any designer fluid in the procedure which is akin to plasmapheresis for example some patients and their goal plasmapheresis where we need to remove reactive antibodies or toxins where their plasma is being thrown out and replaced with physiological fluids such as saline and an album.

So if you could do exactly the same procedure and animals but analyze the effects on tissue rejuvenation on muscle, liver and brain, which is our typical organs that started.

– Just to clarify for the for our audience. If I could um whole blood contains plasma plus the red blood cells and clotting factors? Plasmapheresis is a technique where um the where you take plasma where the red blood cells have already been removed.

But the plasma you can with plasmapheresis selectively remove certain of the molecular protein components in the fluid and varying amounts. And that's what you began doing to try and tease out exactly what it was in the plasma that was creating these these wonderful effects. – And thank you.

Thank you Robert. Very, very good clarification. So yes. So what happens is that we remove 50% of blood plasma, the liquid part of the blood from animals from old mice.

And we replace it with physiologic solution which is salty water, saline and albumin album. And we are not aging extra were simply restoring the album in which is an hour Plasma and so on.

We throw out the old plasma, we throw out the album means we have to add it back and then all of the blood cells. Red blood cells, platelets and Luke aside.

White blood cells are returned back to the same animal. So we do not change the age of the cells that circulate in blood. We are simply diluting by 50% all of the proteins which circulate in the blood.

That's all is done physically. And what we discovered is that that procedure is more rejuvenated than any other approaches that were published including para bio sis or young blood fractions or sin analytics or any designer specific molecule that process.

Teacher alone of diluting aged serum proteins make old mines statistically the same as young when we measure their neurogenesis formation of new neurons in hippocampus, the area of the brain which is responsible for memory and learning and also reduces liver fibrosis and I'd capacity and also improves muscle repair without fibrosis.

And it also restores the positive adaptive immunity and reduces the number of circulating senescent cells and the number of DNA damage cells in pilot human studies that you published more recently. So I mentioned that this procedure that we miniaturized and animals is analogous to human procedure that is already FDA approved.

So with in a collaboration with dr debris Kiprusoff who has his private clinic in no bottom we we did that we

performed pilot studies with humans where we decided to see if tripitaka plasmapheresis is rejuvenated and what published most recently in november of this year.

Sorry, not in november this year, just a couple of a couple of months ago um I think it was end of december, I can tell you specifically or we can look it up.

So what you published recently is that um when we analyzed the protium of people who performed rounds of this procedure we noticed that there was significant rejuvenation of numerous circulatory proteins and these proteins were rejuvenated not just after their diluted but stable e several weeks and several months after the procedure.

And furthermore, there was improvement in the composition of myeloid versus lymphoid circulating cells. Also, several months after the procedure which is extremely important, particularly in the situation of global pandemics and knowing that the raging people usually lose adaptive immunity and then there is excess of inflammatory circulating cells.

So this kind of where the outcomes where we show that there is evolutionary conservation in what drives aging and what drives rejuvenation and miles as well as in people. It seems that the aging is not driven by declining young factors. It is driven by the excess of old factors in our blood plasma and rejuvenation is identically driven by diluting these old plasma factors.

Plasma Dilution and Human Studies

– It's so exciting the possibility of using this in humans if you're already doing because the the the techniques you've mentioned the the blood, that the blood removal plasmapheresis replacement with albumin and and all these are all accepted safe medical procedures that have been around for a long time. So um what what have you seen in these patients?

What specific things have you seen in these patients? Have you measured any biological clocks? Like some of the DNA methylation clocks or what other phenotype of aging have you measured? Uh that would show that there's a positive effect with this transfusion technique? – I thank you for asking.

So we have developed our own direct measurement of biological age which is based on the biological noise. I don't know if your audience is familiar with out but um there were there is a phenomena of biological noise increase with age such as that If you measure level of any particular marker or protein even interleukin six, then the levels will vary in human population. And we cannot really predict based on the level of that protein person is younger. But if you measure the variation In interlocking six, young people will have very very small variation and old people will have huge variation or noise in that protein. And so that was known for a while.

But we managed to apply this general knowledge to a new measurement of biological age where we identified specific 10 protein biomarkers or do detectors of biological age based on how noisy they become when we compare young people to old people.

So we published that particular measurement of biological age and the same the same measure of biological age then demonstrates that if people have a disease for example mild cognitive impairment, their age becomes higher based on our I wouldn't call it clock, I don't think that this clock and I will tell you why.

But I don't know. Let's let's call is just a measure measure abolish college and then when people undergo rounds of tribunal plasmapheresis for every single participant, biological age was decreased and that is direct measurement.

It is not a prediction based on artificial intelligence. We're actually measuring person's age similarly to how you would measure their weight. If you have skills and you know that the way it could be measured on scales.

So that so that is also published in the same paper which collaborates the Dr. Keep Rov and also Professor Joe Kramer who is the director of UCSF Brain aging Center.

So that is the big collaborative work that came out recently that work demonstrated that humans biological age can be measured and then it is decreasing after rounds of plasma phrases.

And I have many many I know um cardiac. So I would like to discuss about just idea of linear progression of biological age, idea that DNA methylation clocks measure biological age when they actually predict not measure age and what they predict is chronological age. It's not biological age.

They are trained on your chronological age as the input and they give you back your chronological age. And most importantly, even for any measurement including for our measurement which is a measurement of biological age, we only can tell you what is biological age of your peripheral blood cells.

P. B. M. C. S. It doesn't mean that the whole you is of that age. None of our none of our analysis tell you what the entire person biological age is. In fact if I had to guess my guess would be that it is those clinically applicable analysis like cholesterol level blood pressure body mass index.

Um E. K. G. Things which which physicians do will measure biological age the best. – Before you mentioned one other factor of brain size. Was that just in the hippocampus mainly that you saw improvements in brain size Or was that overall brain? – It is not brain size. It is specifically activity of few clusters of brain stem cells. Brain procure sir or neural precursor cells which can divide even when, when they are old and certainly when they are adults and when they are old and then they can differentiate and form new neurons.

So when we're learning how to do skiing or new language or a song or we try to write poetry. Some areas in our brain and hippocampus are making new neurons and those neurons are integrating into the circuitry at least.

That's one of the high priestesses. So one might not necessarily see that you have this bigger. But in animals we can section the brain and we can look at those cells and see how they behave before versus after dilution of all plasma – perhaps through BDNF or some other factors that we've talked about before on the program.

– Oh yes and absolutely. So thank you again for mentioning this part. How does it work? Right. So what we believe is going on is that when the days you have too many proteins of a particular kind, they not only damage us themselves, but they inhibit the positive factors and genes from being present such as be dinner or many other mob Kinney signaling pathway determinants by positive factors. So um so what happens when you dilute h elevated inhibitors, you start recovering your useful gene expression because the genes did not disappear from your genome that are still in your blueprints.

They simply cannot be expressed and made into proteins. And then once the age elevated inhibitors are dropped down by physical dilution. Then person recovers all of the useful proto that people try to figure out what are those proteins and how can we add them back? In theory they are added back naturally because the age elevated inhibitors are dropped down.

– Yeah, this this mechanism you described is fascinating that the old blood has negative factors in getting rid of those actually improves longevity. Several people have advocated donating blood on a regular basis as a longevity thing that people live longer who donate blood. Would that would that work through this mechanism? At least partially.

It's not as good as the full thing. – Yeah, I don't know. I'm absolutely fascinated. I receive numerous emails daily asking if donation of plasma not blood, but plasma right will be rejuvenated.

And I'm looking forward to conducting the studies. My gut feeling that it will be somewhat positive and I would love to know what would be the suggested intervals and and what would be the positive, what would be the outcome. I think it should be absolutely studied if it could be applied to improving human health and again they are not, we're not talking about living forever. We are talking about being held there for many more decades. The plasma donation would be milder.

– They really are not as invasive distributed plasma phrases. And what are the dangers of this technique that you're

describing in Other words?

Biological Age Measures and Safety

Are there certain people that shouldn't take it like history of cancer or a history of heart disease? Alzheimer's or there, What's the downside to it?

It sounds like it's a win win. – I know, but but you you have to remember in your audience remember that this procedure was approved for very serious illnesses.

When we talk to various clinicians in their initial opinion, plasmapheresis is a highly invasive procedure that they even hesitate to uh to prescribe to the patients who are sick.

And now we're talking about relatively healthy young people who would like to do it to become healthy and young for longer. Right? Um so, so there are no known side effects which are published and they're also probably unknown side effects which are not yet studied because the procedure was not broadly used in relatively healthy adults.

The one thing that that that comes to mind is that we are either filtering plasma away from cells. So there is some sort of filter or marsh, which stops our blood cells or cells are physically removed to go through the tubing and spun down and return back.

So these procedures probably are damaging to blood cells and that damage probably accumulates after rounds of procedures. And that that one thing that comes to mind.

Another thing is that there is suggested side effect of activation of complement proteins and complement are those little proteins which can assemble and form perforations and blood vessels. They actually form perforations in pathogens.

That's how they vote. But if they are activated and appropriately they can form perforations in our own cells of the blood vessels. So, so that is another kind of known kind of not very, not very good side effect plasmapheresis. I have to ask, have you tried the procedure on yourself? No, I did not try the procedure on myself.

Another did my convoy. So but we we got we got some volunteer responses from people who did, who told us that they feel more energetic and at the same time they feel that, you know, they feel called that some sort of balance has been achieved in their body and their brain kind of reacts to that. So that was kind of, you know, just um just a gossip, gossip, anecdotal evidence.

– Do you see this as eventually becoming available widespread for people to go in and get this or or their their practical limitations to it, do you think? – I don't know.

I don't know how to characterize it. For me. It was just a scientific exploration. I never looked at it as, okay, this is the final we discovered or idea how to become younger and how they're in fact, when I look at the kind of from rational point of view, I don't think that people will become younger simply by performing rounds of plasma for races unfortunately, but that opens another door for us to understand why the illusion of our plasma is so robustly and so quickly rejuvenated.

What are they actually doing? Mechanistically or scientifically And eventually for me, the path is through developing pharmacology, developing Afghanistan Afghanistan approaches which do what plasmapheresis has told us we should be doing. So I don't like it.

Maybe not the most, you know, um optimistic evaluation. I know that and I might be incorrect, but this is just my opinion. – You mentioned Dr. Dubrov is does he do this work in his clinic now?

Is it currently available in some form? – It's not only in his clinic, what I have learned um that many clinics now

throughout the country are offering this service and there are some anti aging enthusiasts who are doing, who are paying for the service And who are performing plasmapheresis on themselves.

And because the services offered by certified physicians, I guess I'm not very much concerned because they are not, they know what they're doing. For example, Dr. Dubrov was doing plasma phrases for over 25 years, so they know what they're doing but I think that more studies should be done on the outcomes of plasmapheresis before, more people just jump on this wagon.

You know, it's not really the same as doing Botox or things which are cosmetic. Again, it is my opinion on my character incorrect. I have no training in medicine whatsoever. So my opinion is just that of a scientist.

– Absolutely. We really appreciate your opinion. I want to be respectful of your time and perhaps before we leave you could tell our audience the best way that they can, they can reach your website or follow you on social media. – Yes. So, um, so if you have laboratory website can go a lab, you can easily see what we are doing. Feel free to send me an email.

I am barraged by emails but I'm trying to reply to everyone every email. And uh, and also if you are in the Berkeley area then send me an amount perhaps a scheduled visit to the canvas lab. – Excellent. Well, well, thank you Arena so much for taking an hour from your busy schedule to spend with us today and talk about the fascinating work that you're doing in your lab.

– You're welcome. Thank you for highlighting our field of science. Bye bye.